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REVIEW

The inflammatory perspective of depression in the context of chronic medical conditions

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Abstract

Background: The inflammatory hypothesis of depression implies that an unbalance of the immune system may trigger abnormal responses, affecting neural signalling mediators and the hypothalamic-pituitary-adrenal axis. This theory underlies a bidirectional hypothesis on the influence of depressive symptoms in the clinical course of chronic inflammatory disorders (CID), as well as in the genesis of mood disturbances. We aim to review current knowledge on depressive disorders and chronic inflammatory diseases as comorbidities and the underlying pathophysiologic mechanisms.

Methods: We performed a bibliographic search in PubMed, including publications released in the last 5 years, written in English, Portuguese and Spanish, containing the key words: depression, chronic inflammatory disorders, psoriasis, arthritis, inflammatory bowel disease and multiple sclerosis.

Results: According to the literature, the incidence of depressive disorders is significantly higher in patients with CID. The medical conditions also present a worse clinical progression, with more frequent flares and decreased response to treatment. At the cellular and biochemical level, there is a deregulation of innate and adaptive immune responses, common to both medical and psychiatric pathologies, as well as an increase of the pro-inflammatory and acute phase reactants, with a inhibition of anti-inflammatory mechanisms. CID exert a major impact on the patients, at social, relational, functional and working levels, leading to decreased global performance, and enhancing several risk factors for depressive disorders.

Conclusion: Besides the life stressing factors associated to CID, there are cellular and biochemical alterations triggering the dysfunction of the immune system, establishing a bridge with the pathophysiology of depressive disorders.

Keywords: Depression, Chronic inflammatory disorders, Psoriasis, Arthritis, Inflammatory bowel disease, Multiple sclerosis.

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Introduction

According to the World Health Organization, depression affects more than 350 million people of all ages worldwide, being the leading cause of disability and a major contributor to the global burden of disease (WHO|Depression.2012). Depression is associated with adverse outcomes including increased mortality, increased morbidity, poor health-related quality of life and increased healthcare use and costs [1]. It affects people of all ages and social status and has a major impact on social, professional and interpersonal functioning. Major depressive disorder may be approached as a group of diseases, rather than a single clinical entity, since there are several different clinical presentations. Overall, depression is characterized by a general feeling of sadness, lack of pleasure or interest in activities, changes in weight and appetite, sleep disturbances, difficulty in concentrating and feelings of worthlessness and hopelessness. Suicidal ideation may or may not be present (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition).

Pathophysiology of depression is complex and depends on the interaction between several systems. The role of the neuroendocrine system, in particular the hypothalamus-pituitary-adrenal axis, and the influence of the immune system have been the subject of intense research. Nowadays, there is ample evidence to support a role for inflammation as an etiopathogenic factor in mood disorders even though the exact mechanisms remain unexplained [1, 2].

Depression has been associated with an increase in systemic levels of inflammation biomarkers, including C-reactive protein (CRP), interleukin (IL)-1, IL-6 and tumor necrosis factor alpha (TNF-α) in clinical and community populations [1, 3-6], as well as increased number of circulating leukocytes, which could be the source of cytokines [6]. Also, depressed patients have increased production of positive acute phase proteins (APPs) and decreased production of negative APPs [7].The main immune cell in the brain is microglia, the tissue resident macrophages of the brain, and that is known to react to peripheral inflammation[8] and also to be involved in inflammatory responses to neuronal damage in the brain [6, 9].

Recently, IL-17, which works as a mediator of communication between immune cells and tissue, has been given particular attention. Although findings regarding a specific role for this cytokine are not conclusive yet, a recent study described a direct correlation between type 17 T-helper cells (Th17) and depression sensitivity [10]. In this study, administration of Th17 cells, resulted in increased sensitivity to depression in two different mice models. Furthermore, mice lacking RORγt, the transcription factor essential for Th17 cell development, were less prone to develop depression [10]. This probably indicates that Th17 cells have the capacity to directly affect target cells in the CNS, possibly through IL-17 (for review see The role of IL-17 in CNS diseases [11]).

It has also been reported that levels of zinc (an antioxidant) are reduced in patients with depression [12, 13]. In contrast, complement factors C3c and C4, and immunoglobulin M (IgM) and IgG are increased in depressive disorder [14]. Furthermore, therapeutic administration of the pro-inflammatory cytokine IFN-γ in diseases such as hepatitis C and cancer leads to the development of depressive symptoms in up to 45% of participants [15]. Another means by which the immune system activation may play a role in the pathogenesis of mood disorder is by decreasing the peripheral tryptophan (TRP) available to cross the blood-brain barrier [16-18].

In depression there is also a deregulation of a normal adaptive system—the stress system [19]. On the one hand, melancholic depression is characterized by pathological hyperarousal and anxiety, focused on the self, with feelings of worthlessness and hopelessness, regarding personal and professional life, as well as anhedonia. These patients appear to present an activated stress system, with physiological signs of hyperarousal, such as hypercortisolism, suppression of the reproductive and growth hormone axes, with loss of interest in sexual activity, late insomnia, and loss of appetite, being the depressed mood most severe in the early morning. On the other hand, in atypical depression, patients present feelings of disconnectedness and emptiness, with cognitive and mental weariness, social isolation, lethargy, fatigue, excessive sleepiness, increased food intake, weight gain, and depressed affect that worsens as the day progresses (for review see [19]). Furthermore, acute experimental stress or stressful life events can increase IL-6, IL-10, IL-1β, and TNF–α production in response to stimulation by lipopolysaccharide. It can also alter the number and function of CD4 and CD8 lymphocytes and natural killer, as well as modulate platelet function and activation. Such observations allow the establishment of a link between the "stress system" and the immune system, since several inflammatory cells present receptors for hormones of the hypothalamus-pituitary-adrenal axis [20, 21].

All previously stated enables a comparison between depression and auto-immune/auto-inflammatory diseases, which depend on the deregulation of the immune system. In the past years, much has been studied regarding the possible relation between psychiatric disorders and chronic inflammatory conditions. Given that mood disorders are the most frequent of the former, many studies have focused both on the impact of depression in the development and clinical course of chronic inflammatory diseases, as well as on the possibility of the latter promoting the development of mental illness. Recommendations for the management of co-morbidities of psoriasis and RA have recently been issued by the Canadian Dermatology-Rheumatology Comorbidity Initiative, which include 3 recommendation on how to manage depression or depressive symptoms in these patients [22].

This work aims to review the link between depressive disorders and four chronic inflammatory conditions: psoriasis, inflammatory bowel disease (IBD), rheumatoid arthritis (RA) and multiple sclerosis (MS).

Depression and Psoriasis

Psoriasis is a common chronic immune-mediated inflammatory disease, which affects 2–3% of the population. It is histologically characterized by increased proliferation of keratinocytes, as well as by inflammatory leukocyte cell infiltration into the epidermis and the dermis [23, 24]. Pro-inflammatory dendritic cells that produce TNF-α and iNOS are present and capable to polarize both Thelper cells type 1 (Th1) and Th17 cells [25]. Together keratinocytes and immune cells are central to the pathophysiology of the disease, they produce cytokines like IL-6 and transforming growth factor (TGF)-β, which induce maturation of naïve T cells into Th17 cells [26]. Afterwards, IL-23 produced within the skin induces expansion of Th17 cells as well as their production of IL-22, which regulates proliferation and differentiation of keratinocytes [27-30]. These cells also attract neutrophils into the skin, through production of IL-17 [28]. The inflammatory response is amplified through IFN-γ and TNF-α produced by Th1 cells [27] or a subset of Th17 cells [31] in the psoriatic lesions, resulting in the characteristic keratinocyte hyperproliferation [31-33].

Psoriasis patients present a high incidence and prevalence of psychological and social problems, namely a significantly decreased quality of life, increased perceived stress levels, social stigmatization and employment problems, as well as depression and suicidal thoughts [34, 35]. More than 40% meet criteria for probable mood disorders [36] and the prevalence of depression and/or anxiety disorder ranges between 30% [37] and 58% [38]. Moreover, a diagnosis of psoriatic arthritis further increases the likelihood of depression [39, 40]. A couple of recent reports on the relation between psoriasis and psoriatic arthritis and risk of depression in the US showed that psoriasis was significantly associated with major depression, even after adjustment for sex, age, race and co-morbidities, but that disease severity was not found co-related with increased risk [40, 41].

High levels of stress, either psychological or related to significant life events, appear to precede the onset of psoriasis [42], and also to precipitate disease flares [38, 43]. These high stress levels are likely to affect disease via stress responsive hormones released in the circulation or in the skin. Regarding this perspective, evidence supports the existence of a hypothalamo-pituitary-adrenal axis equivalent within the skin. Thus, stress appears to induce the localized secretion of corticotrophin releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and glucocorticoids.

Previous data suggest that the skin, being highly innervated, may play a role as a "diffuse brain" [44], leading to the hypothesis that the inflammatory response observed in psoriasis may not only be limited to the skin, but that psoriasis actually presents as a systemic inflammatory disease. This is associated with increased risk for the development of obesity, insulin resistance, cardiovascular disease, metabolic syndrome and psychiatric comorbidities [45-48]. There are several neuropeptides localized in the skin, namely catecholamines, substance P, calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP) and nerve growth factor (NGF). Psoriatic lesions strongly correlate with the activation of the autonomic nervous system and with increases in many of these neuropeptides [49, 50]. A recent study reports significantly lower levels of systemic Brain-Derived Neurotrophic Factor (BDNF) in psoriasis patients than in matched controls [51]. Moreover, it has been found that psoriatic plaques have increased nerve fiber density and increased expression of a number of neuropeptides [52-55], including sensory cutaneous nerves, leading to the hypothesis that locally secreted neuropeptides contribute to the maintenance of psoriatic disease [52, 56]. Harvima and colleagues[57] observed that psoriasis patients suffering from high levels of psychological stress presented elevated expression of VIP and CGRP in the papillary dermis of lesional skin, with such nerve fibers barely detectable in lesions from low-stress individuals [57].

Another set of data on the pathophysiological link between psoriasis and depressive disorder is based on the response of the psychiatric comorbidity to psoriasis treatment, and vice-versa. Langley et al. [58] observed a significant decrease in depressive symptoms, in a cohort of Canadian and European psoriasis patients, after a 24-week treatment with Ustekinumab (a human monoclonal antibody against IL-12 and IL-23). Studying the effect of adalimumab (an anti TNF-α human monoclonal antibody), Menter et al. [59] also concluded that after a 12 week treatment there was a significant decrease in depressive symptoms/depressive disorder. Also, a recent report shows a link between increased circulating TNF-α in psoriatric patients and increased brainstem serotonin transporter (5-HTT) availability, which responded to anti-TNF-α treatment [60].

Focusing on the improvement of psoriasis after psychiatric treatment, Fortune et al. [61], observed a decrease in the number and frequency of psoriasis symptoms during and in the six months after a short program of cognitive behavioral therapy (CBT). Other types of psychotherapy, including stress reduction and imagery, also have a beneficial effect on psoriatic disease activity [62] .Kabat-Zinn et al. [63]conducted a trial of Mindfulness Based Stress Reduction (MBSR) as adjunct treatment for disease, highlighting that average time to clearance of lesions with UVB for MBSR subjects was 83 days compared to113 for the controls, and for PUVA, 48 days for the MBSR subjects, compared to 85 days for the controls. Furthermore, in several studies, quality of life, fatigue and Psoriasis Area Severity Index scores improved in parallel with depressive symptoms [64].

Given all the aforementioned, it is highly likely that psoriasis and depression present several ethiopathogenic and physiopathological factors in common. This relationship is most probably multifactorial, involving genetic, immunological, neurological and psychosocial risk factors.

Depression and Inflammatory Bowel Disease

IBDs are chronic inflammatory conditions, associated with imbalance of the intestinal mucosa and driven by the cells of the adaptive immune system, responding to self antigens. Crohn's disease (CD) and ulcerative colitis (UC) are the most prevalent and better-known conditions within IBD [65]. In CD, every region of the intestinal tract may be affected; however, it generally affects the ileum and colon, most of the times in a discontinuous pattern. It can be associated with intestinal granulomas, strictures and fistulas. Histologically, the inflammation is often transmural. UC usually involves the rectum and may affect part of the colon or the entire colon (pancolitis) in a continuous pattern. The inflammation is typically confined to the mucosa, and it is usually not associated with intestinal granulomas, strictures or fistulas (for review see Inflammatory Bowel Disease [66]). Patients with IBD are at risk for several other comorbidities, including primary sclerosing cholangitis, ankylosing spondylitis, psoriasis [67] and psychiatric disorders.

The inflammatory response in IBD consists on the infiltration of neutrophils, macrophages, dendritic cells, natural killer cells and B cells and T lymphocytes into the lamina propria of the intestinal wall. This cellular activation induces an increase in local levels of TNF-α, IL-1β, IFN-γ, and cytokines of the IL-23–Th17 pathway [66]. More precisely, in CD there is a predominant Th1 and Th17-type response, where antigen presenting cells (APC) produce increased levels of IL-12, IL-18, IL-23 and TGF-α, wich leads TH1 and TH17 cells to produce TNF α, IL-2, IL-17. All this feeds into a cycle promoting further activation of macrophages, APC and natural killer cells, which together with fibroblasts and endothelial cells will add to the cytokines produced also IL-1, IL-6,IL-8 and IL-12, and triggering the cascade of response [68-73]. In the case of UC, the major response is of the Th2 type, with production of IL-4, IL-5 and IL-13, but there is also a Th17 component[71-74].

Regarding the psychiatric comorbidities in IBD, Román et. al concluded that affective disorders have been extensively studied in patients with IBD, while there are few data on psychotic and other mental disorders [75]. Recently, some studies have suggested that a dysfunctional brain-gut interaction could be involved in the pathogenesis of IBD, namely through: a dysfunction of the autonomic nervous system; abnormalities of the hypothalamic-pituitary-adrenal axis and of the cholinergic anti-inflammatory pathway; a deleterious effect of stress and depression on bowel function; an abnormal coupling of the prefrontal cortex-amygdaloid complex; and an abnormal relation between the microbiota and the brain, which could function as pro-inflammatory factors [76, 77]. In fact, alterations in the forebrain structure have been documented related to pain in IBD, as well as a negative relation between disease duration and the volumes of the subgenual anterior cingulate (sACC), amongst other regions. This may have a considerable impact, since the sACC presents impaired function in major depression [78]. The morphological changes observed in the central and peripheral nervous system in IBD may be due to thromboembolic events, systemic and cerebral vasculitis, and neuropathy and cerebral demyelination due to immune-related mechanisms [79-82].

Evidence to date further suggests a bidirectional link between IBD and mental illness. On the one hand, stress exposure, namely stressful events and perceived stress, appears to potentiate relapse risk in IBD, while on the other hand, active symptomatic disease may exacerbate or even incite stress. At the molecular level both BDNF, whose levels are highly variable in response to stress and vary across brain regions, and glucocorticoids appear to play a role in this link [83]. At the experimental level, induction of depression in a dextran sodium sulfate murine model of colitis was associated with reactivation of inflammation in mice with previously established quiescent chronic inflammation. This effect was partially mediated by an increase in proinflammatory cytokine secretion by macrophages, and prevented by tricyclic antidepressants administration [84]. Goodhand et al. showed that patients presented fewer relapses and steroid treatment in the year after starting an antidepressant than in the year before, possibly pointing to an inflammation-specific benefit from antidepressants[85].

In the case of UC, Cawthorpe D. & Davidson M. observed that in a sample of Canadian patients with a diagnosis of ulcerative colitis, 82% had a mental disorder, and that having mental disorder significantly increased the rate of UC in each year for both men and women [86]. Additionally, they also observed that among psychiatric disorders, neuroses/depressive disorders as a group were significantly more likely to occur before UC for both males and females [86]. It has also been described that Hospital Anxiety and Depression Scale (HADS) depression scores of patients with UC and pouchitis were correlated with mucosal levels of IL-8 (r=0.51; p=0.03) and IL-1β (r=047; p=0.04) [87]. Vlachos et al. showed that, at a molecular level, there was a positive correlation between anxiety and depression scores and the induction of the cytoprotective, antiapoptotic HSP70 in polimorphonuclear cells that are known to perpetuate inflammation in UC patients, alongside with a decreased expression of this protein in the intestinal epithelium, rendering this tissue more susceptible to damage[88].

Focusing on the relation between CD and depressive disorders, Mardini et al. concluded that levels of depressive symptoms were positively associated with future changes in Crohn's Disease Activity Index in a population followed during a 2 year period [89]. Mittermier et al. also described that in CD patients followed for 18 months, there was a significant correlation between Beck Depression Inventory (BDI) scores at baseline and the total number of relapses during of follow-up and that BDI scores at baseline correlated with the time until the first recurrence

of the disease[90]. In line with these findings, Câmara et al. highlighted that the association between perceived stress and exacerbation of CD was completely attributable to the mood disturbances, specifically anxiety and depression [91].Ananthakrishnan et al. showed that depressive symptoms were associated with a 2-fold increase in risk of CD, with both recent and remote (baseline) symptoms playing a role. The effect size of this association was in the same range as those found for current smoking, oral contraceptive use and NSAID use [84].

Looking at the impact of the different treatment strategies for IBD on psychological disorders, it was shown that the risk of depression at 1, 2, and 5 years after surgery for UC or CD (5, 7 and 11% respectively) was similar [92]. More recently, Guloksuz et al. described a decrease in scores of depression scales after anti-TNF-α infusion in patients with CD, which followed the reduction of inflammation (increase in negative acute phase proteins— albumin; and decrease in positive acute phase proteins—a1 and a2 fractions). Moreover the activation of the system was higher in patients with current/past depressive disorder[7].

Given all the aforementioned, it is possible that the deregulation of the immune function, both locally and systemically, may play a pivotal role in the interaction between mood disorders and IBD. It is plausible to consider the potential importance of a biopsychosocial model in the pathogenesis of IBD, implying different approaches to the management and treatment of these patients.

Depression and Rheumatoid Arthritis

RA is an autoimmune disease characterized by joint swelling due to synovial inflammation and hyperplasia; osteoarticular deformity, due to cartilage and bone destruction; production of the autoantibodies rheumatoid factor and anti–citrullinated protein antibody (ACPA), ("deformity"); and systemic co-morbidities, namely cardiovascular, pulmonary, psychological and skeletal [93]. It affects twice more women than men, with the highest incidence of new cases between 50 and 70 years of age. Affected individuals present progressive disability and reduced life expectancy, as well as several difficulties due to the high socioeconomic costs related with this disease [94].

Although the cause of RA remains unknown, it appears to have a multifactorial ethiopathogeny with contributions from innate and adaptive immune responses. In genetically susceptible hosts, various environment-gene interactions may promote the loss of tolerance to self-proteins, namely those that contain a citrulline residue, anti-CCP (anti-cyclic citrullinated peptide, ACPA) and rheumatoid factor (RF). Although presence of these auto-antibodies is currently used in diagnostics, it is important to note that a proportion of patients remain seronegative for diagnostic antibodies [95]. This leads to an anticitrulline response involving both T-cell and B-cell compartments. Regarding T-cells, the proportions of Th1/Th17/Treg subpopulations are altered in the blood of RA patients, with degree of imbalance being correlated with disease stage/severity [95]. As described above, Th17 cells, which are increased in RA patients, produce several inflammatory cytokines, such as IL-17A, IL-17F, IL-21, IL-22 and TNF-α [96, 97]. The innate immune system also participates in this inflammatory cascade, with macrophages and dendritic-cells producingTGF-β and IL-1β, IL-6, IL-12, IL-21, and IL-23, thus providing an environment that supports Th17 differentiation and suppresses differentiation of regulatory T cells [98]. Concerning humoral adaptive immunity, it is fundamental in the pathogenesis of RA and synovial B cells are mainly localized in T-cell–B-cell aggregates, whereas plasmablasts and plasma cells are more widely distributed in the synovium and also in juxta-articular bone marrow [99, 100]. The deregulation of immune responses and imbalance cytokine production activates tissue cells, such as synovial fibroblasts and osteoclasts, disturbing tissue homeostasis, promoting synovial hyperplasia and joint destruction [95].

Among several environmental factors that promote the development of RA, adverse life events also appear to be associated with disease onset. Studies using animal models of inflammation point towards a link between the hypothalamic–pituitary–adrenal axis and cytokine production [101], with neuroimmunologic interactions regulating disease development in rodent models of arthritis. This may be achieved through a local effect, as several neurotransmitters are expressed in synovitis in RA, or through a central pathway, since cytokines are rapidly up-regulated in the hypothalamus during peripheral inflammation [93].

Depression is more common in RA patients than in the general population [102] and has been associated with increased mortality [103], pain, fatigue [104], reduced health-related quality of life [105], increased levels of physical disability [106] and increased health care costs [107]. In a meta-analysis developed by Faith Matcham et al. [108], it was shown that the meta-analytical pooled prevalence of major depressive disorder in RA patients according to the DSM diagnostic criteria was 16.8% (95% CI 10.0%, 24.0%), while dysthymic disorder (according to DSM criteria) presented a pooled prevalence level of 18.7% (95% CI, 2.0%, 39.0%). When considering the prevalence of depression using the self-assessment questionnaire Patient Health Questionnaire, version 9, it was 38.8% (95% CI 34.0%, 43.0%). Although the prevalence of depression disorder is higher in RA than in the general population, it is similar to other chronic and disability diseases [108-111]. Besides possible common endogenous ethiopathogenic pathways, potential causes for the development of depression in RA patients include more advanced age, severe forms of disease, pain, work disability. On the other hand, the presence of depressive disorder/depressive symptoms enhances the subjective negative perception of disease consequences, as well as algic and functional complaints. Furthermore, depression in RA is associated with a higher risk of suicide and mortality [112].

Current clinical treatments for RA aim to relieve signs and symptoms, namely inflammation, swelling and pain; minimize tissue damage; maintain the patients' functionality; and preserve quality of life, reducing premature mortality associated with the condition [113]. Regarding the influence of depression in the management of the rheumatic disease, Matcham et al. reported that on a 2-year follow up study, baseline depression/anxiety status predicted both disease activity and disability across the entire observation period, also reducing response to prednisolone treatment in some patients. They also highlighted that the tender joints count and the patient global assessment were the DAS items most consistently associated with mental health status [114]. However, studies analyzing the effect of RA treatments on psychological symptoms present some discrepancies in the results.

Bae et al. performed an open label study with RA adult patients who showed inadequate response to oral methotrexate (MTX), and concluded that those treated with etanercept (a TNF-alpha inhibitor)+MTX presented a statistically significant decrease in depression compared to those treated with another disease modifier anti-rheumatic drug+MTX [115]. Similar findings were published by Machado et al. using a study design similar to the previous, highlighting a significant improvement in depression [116]. Contrary findings were published by Pinho de Oliveira Ribeiro et al. which concluded that patients treated with biologic drugs had the highest average scores for the signs and symptoms of anxiety, depression, and suicidal ideation, contrary to patients treated with methotrexate and leflunomide who had the lowest averages for all categories. In this study, leflunomide was associated with the lowest scores of both anxiety and depression [113]. Similarly, Kekow et al. reported no significant change in depression scores in patients with early active rheumatoid arthritis treated with etanercept+MTX compared with those treated with MTX only [117]. Despite underlining the importance of future studies in this area, these differences may result from different study designs, as well as different populations and stages/severity of disease.

Given that being female is a risk factor for the development of both RA and depression, Tokunaga et al. studied the sex differences in the effect of RA treatment with a biologic drug on depression and concluded that the level of improvement tended to be larger for female subjects after treatment initiation, namely regarding activities of daily living, quality of life and score on the Hamilton Depression Rating Scale [118].

As with other chronic inflammatory diseases, there appears to be a link between rheumatoid arthritis and depressive disorders, both at an environmental and at a pathophysiological level. These diseases influence each other bi-directionally, interfering with the prognosis and response to treatment. However, evidence in this area is still sparse and future work is needed to clarify the underlying pathways connecting RA and mood disorders.

Depression and Multiple Sclerosis

MS is a chronic autoimmune disease which affects the central nervous system and is characterized by inflammation, demyelination, and neurodegeneration, in the brain and spinal cord [119]. It predominantly affects young adults, twice more women than man, with more than 2.5 million individuals affected worldwide [120]. In 85% of cases MS initially presents either as optic neuritis, transverse myelitis, or a brain-stem presentation, in a young adult aged 20–40, with subsequent spontaneous resolution. This is followed by a relapsing and remitting course and later by a progressive phase. During the intermittent phase, most of the relapses appear to be associated with virus infections. In a lower percentage of cases, it begins with a progressive course [121-126].

MS lesions are denominated plaques. The acute plaque is characterized by a perivascular mononuclear cell infiltration including both CD4+ and CD8+ T-cells, plasma cells and macrophages [127-132]. There is a predominance of macrophage mediated demyelination, as well as loss of oligodendroglia and axons within the lesion [133-135]. Afterwards, oligodendroglial precursors repopulate the plaque and remyelination of new lesions progressively occurs [133, 136]. Chronically active plaques present demyelination and axonal injury, with reactive astrocytes and immunoglobulin deposition[137].

At a cellular and molecular level, several studies have showed that T cells from MS patients are able to recognize different myelin protein targets, including myelin basic protein (MBP) [138, 139], proteolipid protein (PLP)[140], myelin oligodendrocyte glycoprotein (MOG) [141]and myelin-associated oligodendrocyte basic protein (MOBP) [142]. These patients also present auto-reactive CD8+ T cell [143]. Although initially Th1 response was considered the major trigger of MS, recent studies have highlighted the role of IL-17, IL-23 and Th17 cells in the pathogenesis of MS. Cerebrospinal fluid of MS patients has a greater proportion of IL-17-secreting cells [144], and MS patients suffering a relapse present a higher percentage of IL-17-producing memory CD4+ T cells in peripheral blood [145].Within the lesions there is also up-regulation of IL-17 gene expression [146] and increased presence of Th17 cells, namely in perivascular cuffs and borders of active lesions [147]. Humoral immunity cells also seem to play a role in the pathophysiology of MS. Plasma cells, immunoglobulins (Ig's) and activated B cells are present within the plaques [129, 137, 148, 149]. Furthermore, MBP-reactive [150, 151] and MOG-reactive [152] Ig's have been detected in CNS tissue from patients with MS, as well as in MS lesions, along with MOG- and MBP-specific Igcomplexed with myelin within macrophages [153]. B cells may increase neuro-inflammation in MS through direct effects on T cells, or through the secretion of the pro-inflammatory cytokines, for example [154].

During MS clinical course, patients present physical, cognitive and psychological symptoms [155]. Depression occurs in over 50% of MS patients over a life-time, having a 12-month prevalence that is double of general population [156]. It is one of the most debilitating co-morbidities, associated with poor clinical outcomes of MS, namely non-adherence to disease modifying medications [157], as well as loss of employment, absenteeism [158], an increased risk of suicidal ideation and suicide [159-161], cognitive dysfunction [162], leading to an overall reduction in quality of life [163, 164].

Patients with MS may be particularly prone to develop the scenario described in the "learned helplessness" theory. It states that depression depends on the attributions people make regarding events affecting them, specifically that an internal, stable, and global attributional style for negative events makes individuals vulnerable to the development of the psychiatric illness [165]. However, besides the adverse life events associated with MS, which may increase the risk for the development of a depressive disorder, there appear do be some pathophysiological processes common to both clinical entities. This is particularly evident when focusing on the inflammatory and immune alterations previously described. Like depressive disorder, MS also presents an alteration of the cytokine pattern, B and T cell phenotype and function. This underlies the role of the immune system as a bridge between the etiology of a chronic inflammatory condition and the development of a depressive disorder.

Conclusion

From all that was discussed above, on four representative inflammatory diseases, it can be argued that the inflammatory approach to depressive disorders will have a large impact, overcoming the limits of traditional psychiatry. The systemic impact of depression may render a susceptible individual prone to the development of other chronic conditions, as well as decreasing response to treatment and enhancing disease severity. It may be the case of chronic inflammatory diseases, atherosclerosis, cardiovascular pathologies and cancer, among others. Thus, future studies should be upheld in order to clarify the biologic pathways underlying the development of depressive disorders, both alone or as comorbidities, with a goal to implement better clinical practice, increasing therapeutic success. Furthermore, it is important to highlight that patients suffering from chronic conditions should always be evaluated by a mental health specialist, since it may prove fundamental in the prognosis of the primary medical condition.

Abbreviations

ACPA: Anti–citrullinated protein antibody; ACTH: Adrenocorticotropic hormone; Anti-CCP: Anti-cyclic citrullinated peptide; APC: Antigen presenting cell; APP: Acute phase proteins; BDI: Beck Depression Inventory; BDNF: Brain-derived neurotrophic factor; CBT: Cognitive behavioral therapy; CCP: Cyclic citrullinated peptide; CD: Crohn's disease; CD4: Cluster of differentiation 4; CD8: Cluster of differentiation 8; CGRP: Calcitonin gene-related peptide; CRH: Corticotrophin releasing hormone; CRP: C-reactive protein; DAS: Disease activity scale; HADS: Hospital Anxiety and Depression Scale; DMARD: Disease modifier anti-rheumatic drug; HSP70: 70 kilodalton heat shock proteins; IBD: Inflammatory bowel disease; IL: Interleukin; Ig's: Immunoglobulins; IFN-γ: Interferon gamma; MBP: Myelin basic protein; MBSR: indfulness based stress reduction; MOBP: Myelin-associated oligodendrocyte basic protein; MOG: Myelin oligodendrocyte glycoprotein; MS: Multiple sclerosis; MTX: Methotrexate; NGF: Nerve growth factor; NSAID: Non-steroid anti-inflammatory drugs; PLP: Proteolipid protein; PUVA: Psoralen and ultraviolet A therapy; RA: Rheumatoid arthritis; RF: Rheumatoid factor; RORγt: Isoform of the RAR-related orphan receptor gamma; sACC: Subgenual anterior cingulate; TGF: Transforming growth factor; Th1: T-helper cells type 1; Th17: T-helper cells type 17; TNF-α: Tumor necrosis factor alpha; Treg: T regulatory cells; TRP: Peripheral tryptophan; UC: Ulcerative colitis; VIP: Vasoactive intestinal peptide; 5-HTT: 5-hydroxitriptamine transporter

Competing interests

The authors declare no conflict of interest.

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